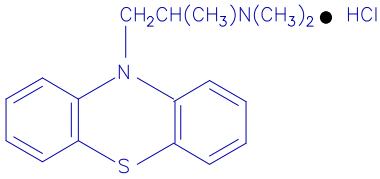
ABSTRACT



PROMETHAZINE HYDROCHLORIDE

CAS No. 58-33-3

Chemical Formula: $C_{17}H_{20}N_2S \bullet HCl$ Molecular Weight: 320.88

Synonyms: Phenothiazine,10-(2-(dimethylamino)propyl)-,monochlorohydrate; 10H-phenothiazine-10-ethanamine; 10-(2-dimethylamino-2-methylethyl)phenothiazine hydrochloride;*N*-(2'-dimethylamino-2'-methyl)ethylphenothiazine hydrochloride **Trade names**: Diprazi; Kinetosin; Phenergan; Phenergan hydrochloride; Promine; Pipolfen; Plletia; Prorex; Promantine; Pyrethia; Romergan hydrochloride

Promethazine hydrochloride is a drug used for the management of allergic conditions, motion sickness and nausea, and as a sedative to treat psychiatric disorders. This drug was nominated for testing by the Food and Drug Administration because of its widespread use in human medicine and because of lack of data on its potential carcinogenicity. Oral administration is the most common route of human exposure. Toxicology and carcinogenicity studies were conducted by administering promethazine hydrochloride (>99% pure) in distilled water by gavage to groups of male and female F344/N rats and B6C3F$_1$ mice for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, in cultured Chinese hamster ovary cells, and in *Drosophila melanogaster*.

16-DAY STUDY IN RATS

Groups of five male and five female rats received 0, 18.5, 55.5, 166.5, 500, or 1,500 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for a total of 12 doses in a 16-day period. All rats receiving 1,500 mg/kg, four males and four females receiving 500 mg/kg, and one male and one female receiving 166.5 mg/kg died during the study. No deaths occurred in the remaining dose groups. Final mean body weights of rats receiving 166.5 mg/kg were significantly lower (12% to 25%) than those of the controls. Clinical findings included decreased activity, ocular discharge, and labored breathing in males and females receiving 166.5, 500, and 1,500 mg/kg as well as tremors in females receiving 166.5 and 500 mg/kg. There were dose-related increases in the absolute and relative liver weights of rats. Focal suppurative inflammation occurred in the nose of some male and female rats receiving 55 or 166.5 mg/kg and in the trachea of some male and female rats receiving 166.5 mg/kg.

16-DAY STUDY IN MICE

Groups of five male and five female mice received 0, 18.8, 37.5, 75, 150, or 300 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for a total of 12 doses in a 16-day period. Two females receiving 75 mg/kg, one male and one female receiving 150 mg/kg, and four females receiving 300 mg/kg died during the study. No deaths occurred in the remaining dose groups. Final mean body weights of mice receiving promethazine hydrochloride were similar to those of the controls. However, in male and female controls, the final mean body weights were 11% to 12% lower than the initial mean body weights. Clinical findings occurred as early as the first day of the study and included decreased activity in male and female mice receiving 150 and 300 mg/kg. Tremors occurred in one male and five females in the 300 mg/kg group on day 1 and in one male in the 150 mg/kg group and five males and one female in the 300 mg/kg group on day 2. Absolute and relative

liver weights of male mice receiving 75, 150, or 300 mg/kg were significantly greater than those of the controls. No chemical-related lesions were present in male or female mice.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats received 0, 3.7, 11.1, 33.3, 100, or 300 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for 13 weeks. One female receiving 100 mg/kg and six males and nine females receiving 300 mg/kg died during the study. No deaths occurred in the remaining dose groups. Final mean body weights of male rats receiving 100 or 300 mg/kg were significantly lower (19% to 22%) than those of the controls. Mean body weight gain of females receiving 100 mg/kg was significantly lower (14%) than that of the controls. Clinical findings in rats included hunched posture and labored breathing. Absolute and relative liver weights of males receiving 11.1, 33.3, 100, or 300 mg/kg and females receiving 33.3 or 100 mg/kg were significantly greater than those of the controls. Focal suppurative inflammation of the nose and trachea occurred with an increased incidence in rats receiving 100 and 300 mg/kg. A dose-related increased incidence of vacuolar degeneration of the nasal olfactory epithelium occurred in male and female rats that received 11.1, 33.3, or 100 mg/kg.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice received 0, 5, 15, 45, 135, or 405 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for 13 weeks. One control female, one female receiving 5 mg/kg, two females receiving 45 mg/kg, four females receiving 135 mg/kg, and all mice receiving 405 mg/kg died during the study. No deaths occurred in the remaining dose group. Final mean body weights of mice receiving 135 mg/kg were significantly lower (8% to 9%) than those of the controls. Clinical findings of toxicity included labored breathing and decreased activity in one 135 mg/kg female. Absolute and relative liver weights increased in a dose-related trend in both sexes. No chemical-related lesions were observed in mice.

2-YEAR STUDY IN RATS

Based on mortality and body weight differences observed at higher levels, doses of promethazine hydrochloride selected for the 2-year study in rats were 0, 8.3, 16.6, and 33.3 mg/kg. Groups of 60 male or 60 female rats were administered promethazine hydrochloride in deionized water by gavage once daily, 5 days per week for up to 103 weeks. Up to ten male and ten female rats per dose group were evaluated at 15 months.

Survival, Body Weights, and Clinical Findings

There was a significant dose-related decrease in survival of rats. The survival rates in the 16.6 and 33.3 mg/kg male groups and in the 33.3 mg/kg female group were significantly lower than those of the controls. The final mean body weight of male rats receiving 33.3 mg/kg promethazine hydrochloride was 10% lower than that of the controls. Final mean body weights of female rats in the 16.6 and 33.3 mg/kg groups were 9% and 11% lower than that of the controls, respectively.

No chemical-related clinical findings were noted in any dose group. Significant increases in the absolute and relative liver weights of mid- and high-dose female rats and the relative liver weights of mid- and high-dose male rats were observed at the 15-month interim evaluation. There were no biologically significant differences in the hematology or clinical chemistry parameters measured at 15 months.

Pathology Findings

No neoplasms that could be attributed to promethazine hydrochloride administration were found in male or female rats. Several neoplasms occurred with a significantly decreased incidence in rats receiving promethazine hydrochloride. These included adrenal medullary pheochromocytoma (benign or malignant) and pituitary gland adenoma in the 33.3 mg/kg males and uterine stromal polyp in the 33.3 mg/kg females. The decreased incidences of adrenal medullary pheochromocytoma were chemical related. The decreased incidences of pituitary gland adenoma and uterine stromal polyp may have been related to chemical administration. Diffuse fatty change of the liver of male rats increased with dose and was attributed to chemical administration.

2-YEAR STUDY IN MICE

Based on mortality and body weight differences observed at higher levels, the doses of promethazine hydrochloride selected for the 2-year study were 0, 11.25, 22.5, and 45 mg/kg for male mice and 0, 3.75, 7.5, and 15 mg/kg for female mice. Groups of 60 male or 60 female mice were administered promethazine hydrochloride in deionized water by gavage once daily, 5 days per week for up to 103 weeks. Up to 10 male and 10 female mice per dose group were evaluated at 15 months.

Survival, Body Weights, and Clinical Findings

Survival of mice receiving promethazine hydrochloride was similar to that of the controls. Mean body weights of mice were within 7% of those of the controls throughout the study. There were no chemical-related clinical findings in male or female mice. There were no differences in hematology or clinical chemistry parameters measured at 15 months that were attributed to the administration of promethazine hydrochloride.

Pathology Findings

There were no neoplasms or nonneoplastic lesions that were attributed to the administration of promethazine hydrochloride.

GENETIC TOXICOLOGY

Promethazine hydrochloride did not induce gene mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537, or a significant increase in chromosomal aberrations in cultured Chinese hamster ovary cells; both of these tests were conducted with and without exogenous metabolic activation (S9). A small dose-related increase in sister chromatid exchanges was observed in cultured Chinese hamster ovary cells in the presence of S9; this response was considered to be equivocal. No increase in sister chromatid exchanges was observed in the absence of S9. Promethazine hydrochloride did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* administered the chemical by feeding or injection.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of promethazine hydrochloride in male or female F344/N rats receiving 8.3, 16.6, or 33.3 mg/kg. There was *no evidence of carcinogenic activity* of promethazine hydrochloride in male $B6C3F_1$ mice receiving 11.25, 22.5, or 45 mg/kg. There was *no evidence of carcinogenic activity* of promethazine hydrochloride in female $B6C3F_1$ mice receiving 3.75, 7.5, or 15 mg/kg.

The decrease in the incidences of adrenal medullary pheochromocytoma in male rats was considered to be related to promethazine hydrochloride administration. The decrease in the incidences of pituitary gland adenoma in male rats and uterine stromal polyp in female rats may have been related to promethazine administration.

Promethazine hydrochloride also caused an increased incidence of fatty change in the liver of male rats.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Promethazine Hydrochloride

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 8.3, 16.6 or 33.3 mg/kg in water by gavage	0, 8.3, 16.6 or 33.3 mg/kg in water by gavage	0, 11.25, 22.5 or 45 mg/kg in water by gavage	0, 3.75, 7.5 or 15 mg/kg in water by gavage
Body weights	High-dose group lower than control	Mid- and high-dose groups lower than control	Dosed groups similar to control	Dosed groups similar to control
2-Year survival rates	23/50, 18/50, 9/50, 10/51	32/49, 34/50, 31/50, 24/51	39/50, 44/50, 40/50, 44/50	39/50, 42/50, 39/49, 41/50
Nonneoplastic effects	Liver: diffuse fatty change (4/50, 5/50, 16/50, 28/51)	None	None	None
Neoplastic effects	None	None	None	None
Levels of evidence of carcinogenicity	No evidence	No evidence	No evidence	No evidence
Decreased incidences	Adrenal medulla: benign or malignant pheochromocytoma (16/50, 12/50, 9/49, 4/50) Pituitary gland: adenoma (16/50, 16/50, 16/48, 8/50)	Uterus: stromal polyp (10/50, 6/50, 4/50, 1/53)	None	None

Genetic toxicology

Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA97, TA98, TA100, TA1535, and TA1537
Sister chromatid exchanges	
Chinese hamster ovary cells *in vitro*:	Equivocal with S9; negative without S9
Chromosomal aberrations	
Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Sex-linked recessive lethal mutation in *Drosophila melanogaster*:	Negative administered in feed or by injection